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Traumatic Brain Injury and Hyperbaric Oxygen Therapy: Dawn of a New Day

APWCA 16th Annual National Clinical Conference
7-9 Sep 17

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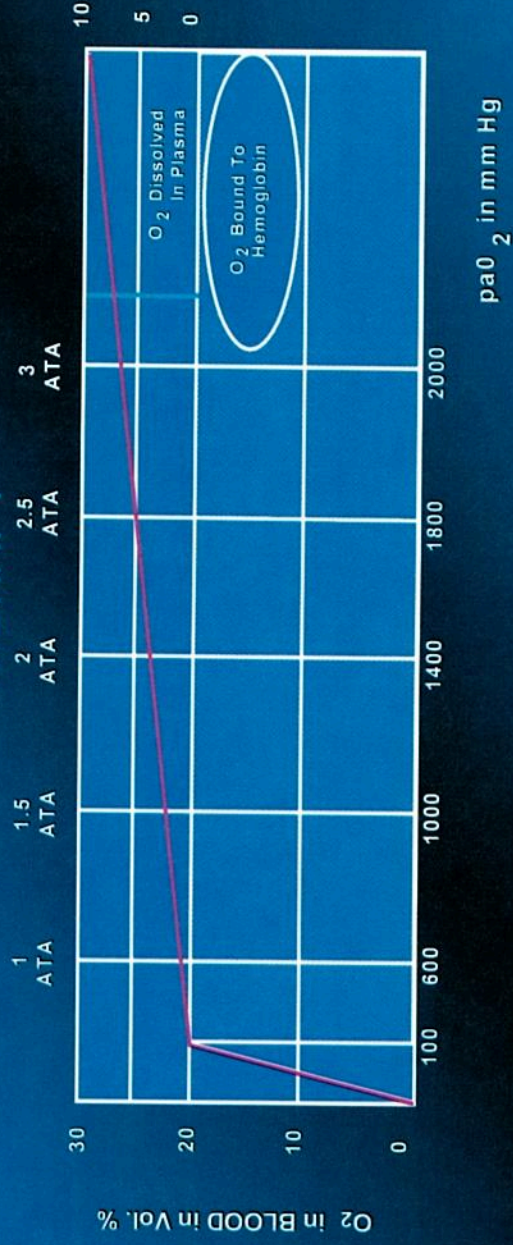
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Disclaimer

- The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02_AFI 40-402

HYPERBARIC OXYGEN THERAPY



Statistics

- 1.4 million TBIs occur annually in the US
- Mild traumatic brain injury: incidence of 180/100,000 population
- Department of Defense: 361,092 TBIs for period Jan 2000 through Dec 2015 with 297,478 mild TBI

http://dvbic.dcoe.mil/sites/default/files/DoD-TBI-Worldwide-Totals_2000-2016_Feb-17-2017_v1.0_2017-04-06.pdf

AHRQ Comments

- Agency for Healthcare Research and Quality:
 - the uncertainty about the frequency and severity of serious adverse events underlies much of the controversy about HBOT
 - the case against HBOT is based on the reasoning that, *because HBOT may be harmful, it must be held to the highest standard of proof*
 - if HBOT can be shown to be as safe as its supporters believe it to be, the standard of proof of its efficacy can be lowered

- AHRQ, U.S. Department of Health and Human Services; 2003 September. AHRQ Publication No. 03-E050:59-62.

Materials and Methods

- Exposures include sham (1.3 ATA air) and treatment profile (2.4 ATA 100% oxygen) – 25/group
- Each group to have 30 exposures
- History and physical done prior to exposures
 - Focused on concussion history and baseline symptoms
- Composite scores obtained prior to intervention, after every 5 exposures and at 6 week follow-up
 - ImPACT
 - Braincheckers (ANAM)
 - PCL-M

Results 1st Publication

- Hyperbaric side effects: no statistical difference between groups with ear and sinus blocks most predominate
 - Included traditional side effects as well as any medical issue that occurred during the study.
- Hyperbaric side effects in a traumatic brain injury randomized clinical trial. UHM 2012, Vol 39 (6) 1075- 1082

AHRQ Comments

- Agency for Healthcare Research and Quality:
 - If there is a 1 percent chance that the treatment works, a rational decision maker would try it—there is a potential gain and no potential loss.
 - On the other hand, if there are proven harms, and their severity and frequency are well described, the probability that the treatment works would have to be higher before most people would try it
- AHRQ, U.S. Department of Health and Human Services; 2003 September. AHRQ Publication No.

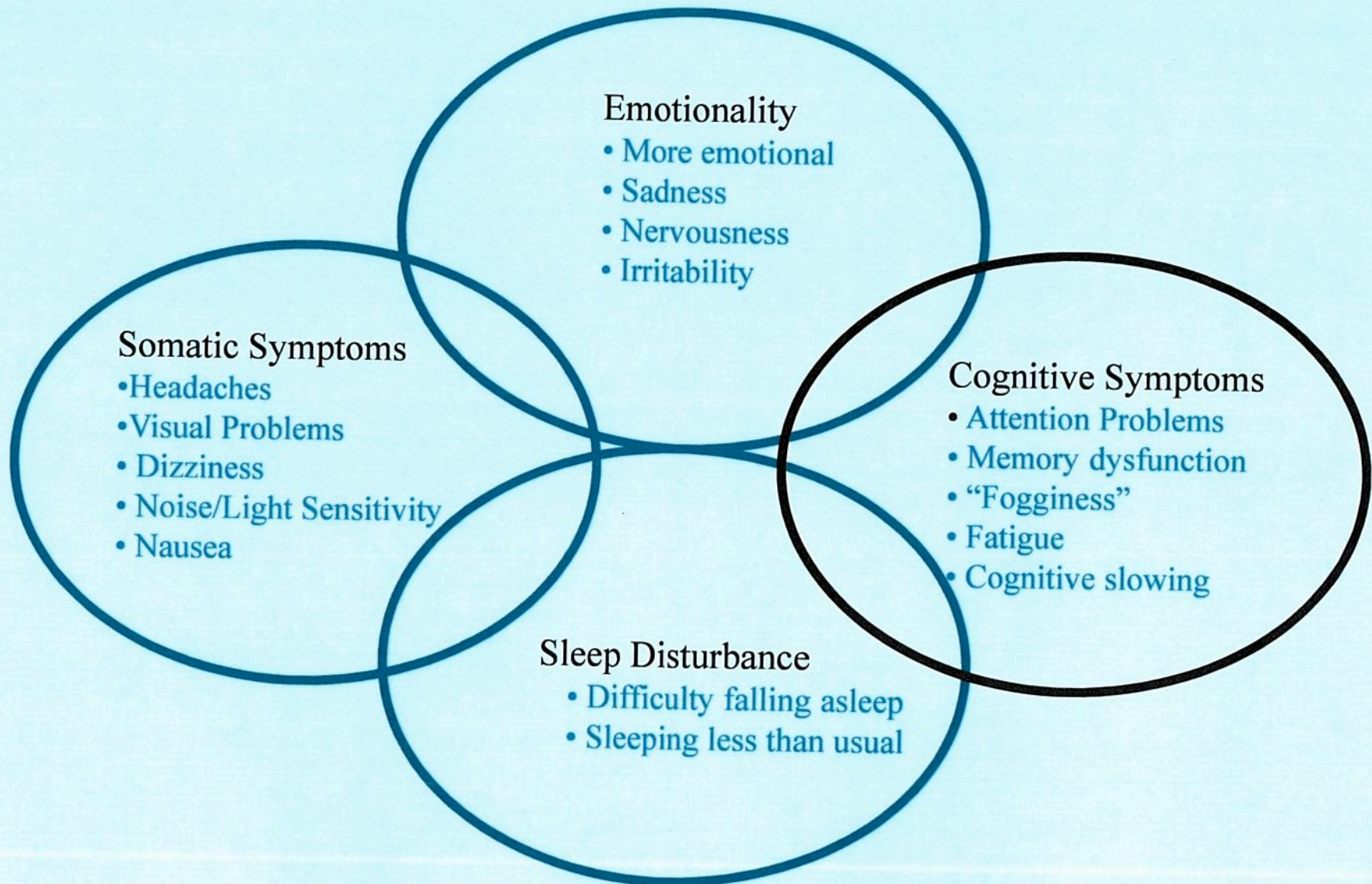
Materials and Methods

- Repeated measures analysis of covariance (ANCOVA)
- repeated measures analysis of variance (RMANOVA)
 - Both used to test for differences between groups
 - No significant statistical difference between groups, but both groups improved
- Relative risk of improvement– ad hoc
 - MedCalc (<http://www.medcalc.org>)
 - Used to analyze responders versus non-responders between each exposure group for each composite score
 - Calculated for concussion history categories

Materials and Methods

- ImPACT: verbal memory, visual memory, processing speed and response time
- Braincheckers (ANAM): code substitution, procedural reaction time, Go-NoGo reaction time, matching to sample, code substitution recall, and simple reaction time
 - Composite score for both speed and accuracy
- PCL-M: composite scores only
- Concussion history: # of concussive events, multiple non-concussive events, two concussive events within 48 hours, time expired from the last concussion to consent , etiology of concussion, and loss of consciousness.

Concussion Symptoms



number	consent	mult	expose	even	Event1	ev to con	Etiology1
7127	May-10	0	0	0	Apr-08	25	1
7256	Mar-10	1	0	0	Jul-07	32	1
7388	Oct-09	1	0	0	Mar-06	43	1
7393	Jan-10	0	0	0	Mar-05	58	1
7469	Mar-10	1	0	0	Mar-08	24	1
7556	Jul-09	0	0	0	Nov-08	8	2
7650	Jul-07	0	0	0	Feb-07	5	2
7755	Mar-10	1	1	1	Jul-09	8	2
7811	Oct-09	0	0	0	Apr-07	30	1
7971	Oct-09	1	0	0	Jun-07	28	1
7642	May-10	1	0	0	Dec-08	18	1
7717	Aug-10	1	0	0	Jan-06	55	1
7934	Jul-10	1	0	0	Apr-06	51	1
7991	Feb-09	1	0	0	Mar-07	25	1
7172	Apr-09	1	1	1	Nov-07	18	3
7491	Sep-10	1	0	0	Nov-04	70	1
7718	Feb-09	1	0	0	Aug-07	18	1
7816	Feb-09	1	1	1	Apr-04	58	1
7848	Apr-09	1	0	0	Sep-06	29	1
7941	Nov-09	0	0	0	Dec-03	71	1
7972	Aug-10	0	0	0	Jul-06	49	3
7628	Jun-10	1	0	0	Jun-09	12	1
7812	Sep-09	0	0	0	Oct-06	35	1
7817	Jan-10	1	0	0	Feb-06	47	3
7490	Jul-10	1	0	0	Apr-06	51	1
7529	Jun-10	0	0	0	Oct-09	9	3
7575	Oct-09	1	0	0	Aug-07	26	1
7827	Mar-09	0	0	0	Jun-07	21	1
7218	May-09	1	1	1	Jul-07	22	2
7283	Sep-10	1	0	0	Nov-05	58	3
7416	Mar-10	1	1	1	May-08	22	1
7443	Sep-09	0	0	0	Mar-08	18	1
7698	Apr-10	1	1	1	Sep-06	43	3
7161	Feb-10	1	0	0	Dec-07	26	1
7180	Jan-09	1	0	0	Jul-05	42	1
7220	Dec-09	0	1	1	Feb-07	34	2
7228	Jun-09	0	0	0	Apr-04	62	3
7430	Feb-10	1	0	0	Oct-09	4	1
7433	Mar-09	1	0	0	Jun-06	33	1
7727	Sep-10	0	0	0	Apr-06	53	3
7895	Aug-10	0	0	0	May-10	3	3
7900	May-09	1	0	0	Feb-06	39	1
7176	Aug-10	0	0	0	Aug-09	12	1
7258	Jun-10	0	0	0	Dec-08	19	1
7287	Jun-10	0	0	0	Jan-09	17	2
7322	Oct-09	0	1	1	May-09	5	1
7457	May-10	0	0	0	Aug-07	33	1
7696	Oct-09	0	0	0	May-06	41	2

Sham
improved

Sham not
improved

Withdrew

Treatment
not improved

Treatment
improved

ImPACT
processing :
example of
segregated
scores

	# Events	Verbal Memory	Visual Memory	Composite Scores Processing Speed	Response Time
Exposures	Multiple	1	2	3	1
	Single	2	3	4	2
	Close event	3	4	5	3
	Yes	4	5	6	4
Time to Consent	Single event	1	2	3	1
	<1 year	2	3	4	2
	<2 years	3	4	5	3
	2-4 years	4	5	6	4
	>4 years	5	6	7	5
	most recent	6	7	8	6
	<1 year	7	8	9	7
Etiology	<2 years	8	9	10	8
	2-4 years	9	10	11	9
	>4 years	10	11	12	10
	Blast only	11	12	13	11
LOC	Impact only	12	13	14	12
	Both	13	14	15	13
	All Blast	14	15	16	14
	All impact	15	16	17	15
Total	Yes	16	17	18	16
	No	17	18	19	17
	Total	18	19	20	18

Results: ImPACT

- All subjects had significant cognitive problems compared with military population
- ANCOVA:
 - no significant differences between groups at any time point for visual memory, verbal memory or reaction time
 - sham was only marginally higher at 30 exposures than the treatment group
- RMANOVA:
 - visual memory and processing time in both groups indicated improvement in each measurement over time

Results – Brainchecker (speed)

	Braincheckers Reaction Time (Speed)									
	Code Sub	Procedural RT	Go-NoGo RT	Match To Sample	Code Sub Recall	Simple Reaction	1.0 to 1.4	>= 1.5		
# Events										
1										
2							4			4
3										0
4							2	2		4
Exposures										0
Multiple										
Single							1			1
Close event							3			3
Yes										
No							3			3
Consent Time										0
Single event										
< 1 year							2	2		4
< 2 years							3	2		5
2-4 years							1			1
> 4 years							1			1
most recent										
< 1 year							4			4
< 2 years							1			1
2-4 years							2			2
> 4 years							3			3
Etiology										
Blast only							1			1
Impact only							1			1
Both							4	2		6
All Blast							2			2
All Impact							2	1		3
LOC										
Yes							4			4
No										0
Total	5	3	10	2	6	2	3			
	8		12		8	2	3			
RROI 1.0 to 1.49							9			9
RROI > 1.5							11			14
RROI > 50% col or row							3			

# Events	Braincheckers Throughput (Accuracy)				
	Code Sub	Procedural RT	Go-NoGo RT	Match To Sample	Code Sub Recall
Simple Reaction 1.0 to 1.4					>= 1.5
1					3
2					1
3					4
4					8
Exposures					0
Multiple					2
Single					1
Close event					4
Yes					2
No					1
Consent Time					1
Single event					4
<1 year					0
<2 years					1
2-4 years					1
>4 years					2
most recent					5
<1 year					9
<2 years					1
2-4 years					2
>4 years					4
Etiology					8
Blast only					1
Impact only					2
Both					5
All Blast					11
All Impact					2
LOC					4
Yes					1
No					4
Total					1
RROI 1.0 to 1.49					5
RROI 1.5 to 1.99					16
RROI > 50% col or row					7
RROI > 1.5					3
RROI > 1.5					15
RROI > 1.5					13
RROI > 1.5					6
RROI > 1.5					5
RROI > 1.5					1
RROI > 1.5					8
RROI > 1.5					1
RROI > 1.5					2
RROI > 1.5					1
RROI > 1.5					2
RROI > 1.5					4
RROI > 1.5					2
RROI > 1.5					4
RROI > 1.5					1
RROI > 1.5					1
RROI > 1.5					4
RROI > 1.5					8
RROI > 1.5					1
RROI > 1.5					1
RROI > 1.5					5
RROI > 1.5					3
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					11
RROI > 1.5					16
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					5
RROI > 1.5					1
RROI > 1.5					4
RROI > 1.5					8
RROI > 1.5					1
RROI > 1.5					1
RROI > 1.5					5
RROI > 1.5					3
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					11
RROI > 1.5					16
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					5
RROI > 1.5					1
RROI > 1.5					4
RROI > 1.5					8
RROI > 1.5					1
RROI > 1.5					1
RROI > 1.5					5
RROI > 1.5					3
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					11
RROI > 1.5					16
RROI > 1.5					7
RROI > 1.5					4
RROI > 1.5					3
RROI > 1.5					5
RROI > 1.5					1
RROI > 1.5					4
RROI > 1.5					8
RROI > 1.5					1
RROI > 1.5					1
RROI > 1.5					5
RROI > 1.5					3
RROI > 1.5					7
RROI > 1.5					4
RROI &					

Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial – UHM 42 (4) 2015

E. George Wolf, Laura M. Baugh, Christine M. Schubert Kabban, Michael F. Richards, Jennifer Prye

- Individual test scores
 - ImPACT:
 - visual memory and processing speed
 - Braincheckers:
 - speed scores in procedural reaction time and simple reaction time
 - accuracy scores for Go-NoGo and simple reaction time

Results: Braincheckers

- ANCOVA:
 - scores were not significantly different for any measure between sham and treatment groups
- RMANOVA:
 - speed and accuracy scores for code substitution recall, matching to sample, and simple reaction indicated improvement in each measurement over time for both groups

Results – PCL-M

# Concussions	Composite Scores			
	Reliable Change	Significant Change		
1				
2			1	
3			2	
4				
Exposures				
Multiple			2	
Single				
Close event				
Yes			1	
No				
Consent Time				
Single event				
< 1 year				
< 2 years				
2-4 years				
> 4 years				
most recent				
< 1 year			2	
< 2 years			2	
2-4 years				
> 4 years				
Etiology				
Blast only				
Impact only			2	
Both				
All Blast				
All Impact			1	
LOC				
Yes			1	
No				
	5	3	4	2
Total	8	6		
RROI 1.0 to 1.49		RROI > 1.5	RROI > 50% col or row	

Results: PCLM

- ANCOVA:
 - were no significant statistical differences between groups at any time point for the composite scores
- RMANOVA:
 - improvement in each measurement over time for both groups for composite scores
- PCL-M score for clinical changes for RROI
 - 5-9 point score change demonstrates reliable change
 - 10 or greater score change demonstrates significant change

Cognitive function in a traumatic brain injury hyperbaric oxygen randomized trial – UHM 42 (4) 2015

E. George Wolf, Laura M. Baugh, Christine M. Schubert Kabban, Michael F. Richards, Jennifer Prye

- Concussion items
 - PCL-M had significant change in subjects with:
 - more than one concussive event
 - additional multiple non-concussive events
 - initiation of hyperbaric exposures within two years of last concussion
 - an impact etiology
 - Congruent with PTSD as a result of one or more life threatening events

Conclusion

- No significant statistical difference between a sham and HBO at 2.4 ATA in scores from ImPACT, Braincheckers or PCL-M
- Both groups showed improvement in scores
 - Theme for results from all DoD pilot studies thus far
 - Attributed to placebo effect
- Subgroups identified that responded to treatment vs sham
- Hydrostatic pressure has therapeutic findings
 - gene uploading/downloading
 - endothelial cell proliferation
 - Increased neuronal excitability

Conclusion

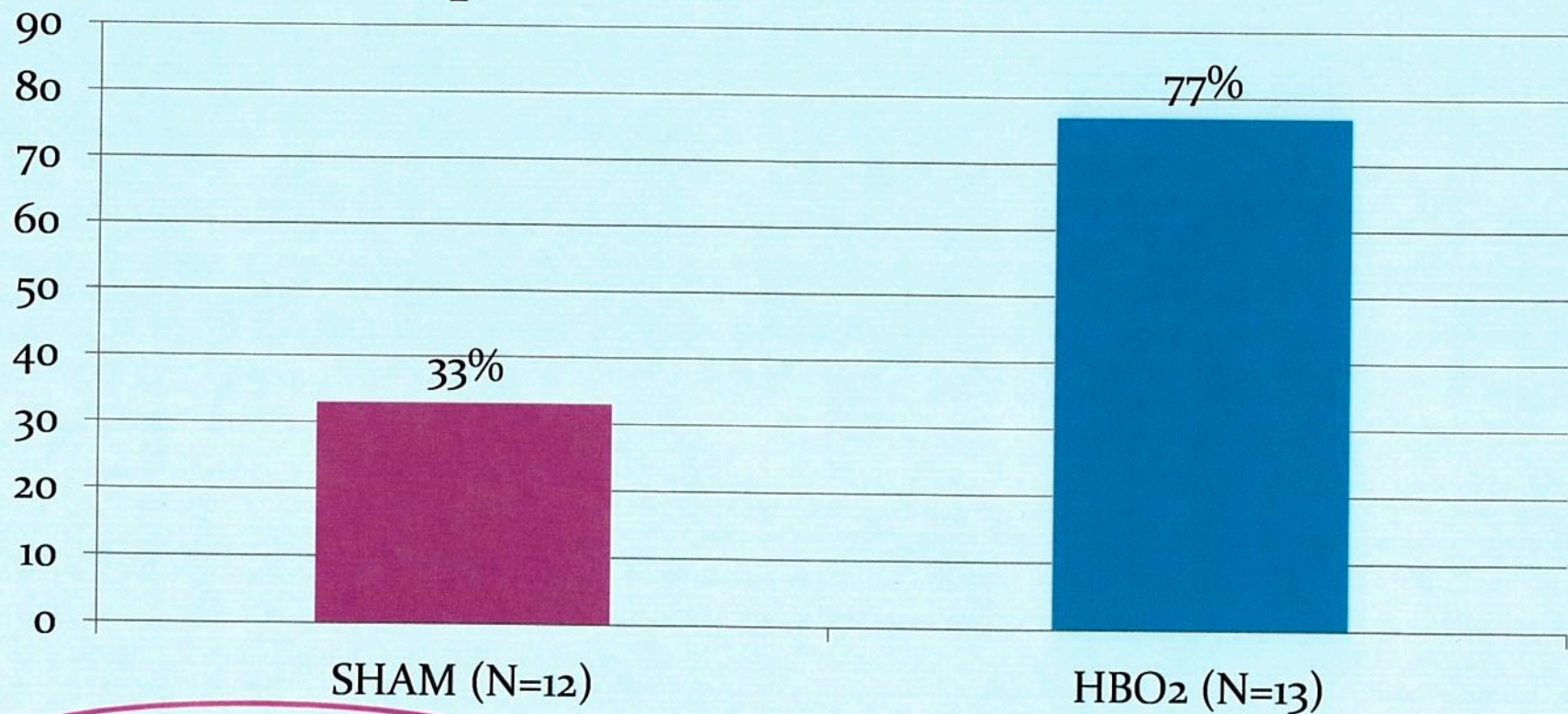
- HBOT appeared safe at a relatively high treatment pressure in chronic TBI subjects
- Data can be used to weigh the risk/benefit consideration when treating TBI patients
 - Definitive data still required
- Per AHRQ, the standard of proof of HBOT efficacy should be lowered

Hypotheses

- PTSD symptoms may respond to HBO₂ treatment
- In those with mTBI who seem to respond to HBO₂ - this response may be due to treatment of concomitant PTSD - rather than mTBI
- Ad Hoc analysis
 - Segregate subjects with PCL-M score >50
 - Analyze those who demonstrated a significant score decrease between treatment and sham groups

PTSD Symptoms[‡]

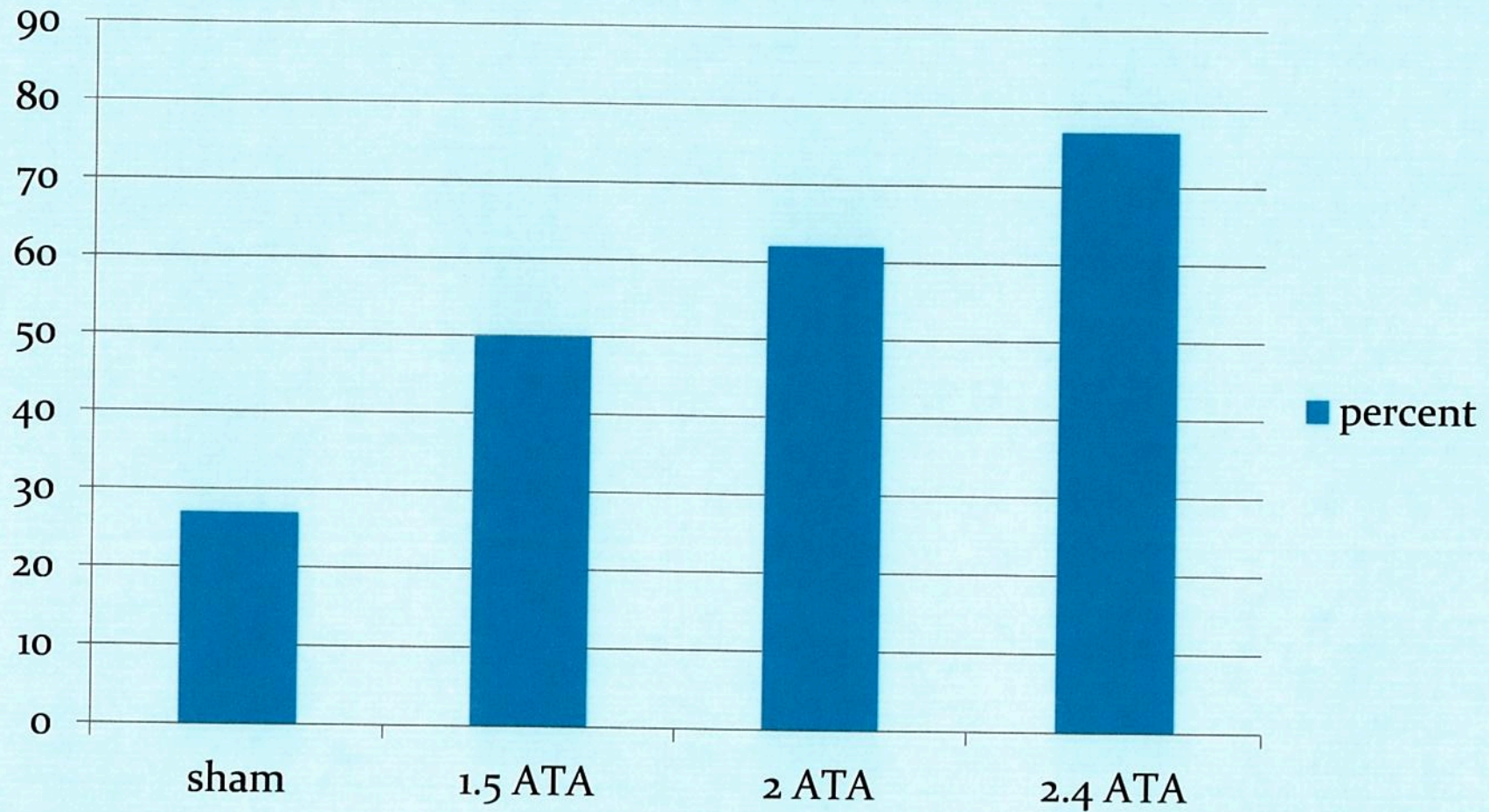
Percentage with **10 or more points**
improvement in PCL-M Scores*



*p=0.028, Chi-Square, 1 DF

[‡] Analysis limited to the "mTBI with PTSD" group

Percentage of subjects responding to therapy pooled data - USN and USAF



Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy – UHM 44 (3) 2017

Sabrina Shandley, E. George Wolf, Christine M. Schubert-Kabban, et al

- Thom reported an increase in the number of CD34+ bone-marrowderived stem/progenitor cells (SPCs) following HBO₂
- Heyboer showed a potential dose-response relation in CD34+ and CD45-dim, with significant increases in patients treated at 2.5 ATA versus 2.0 ATA.

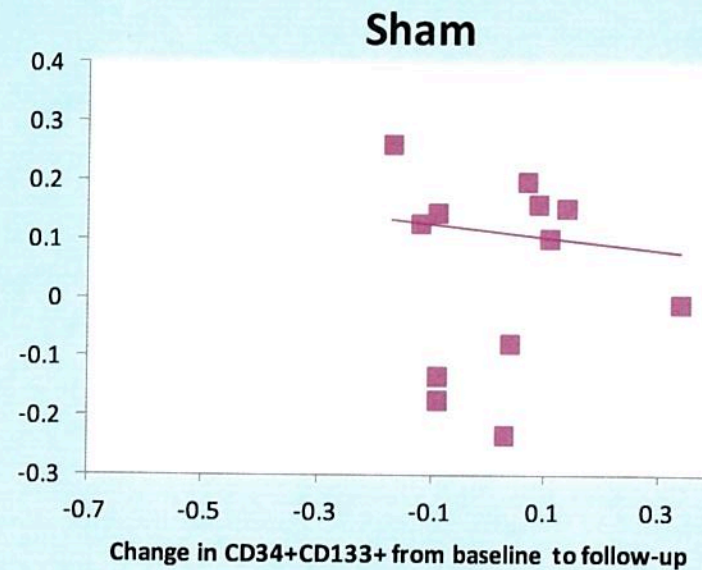
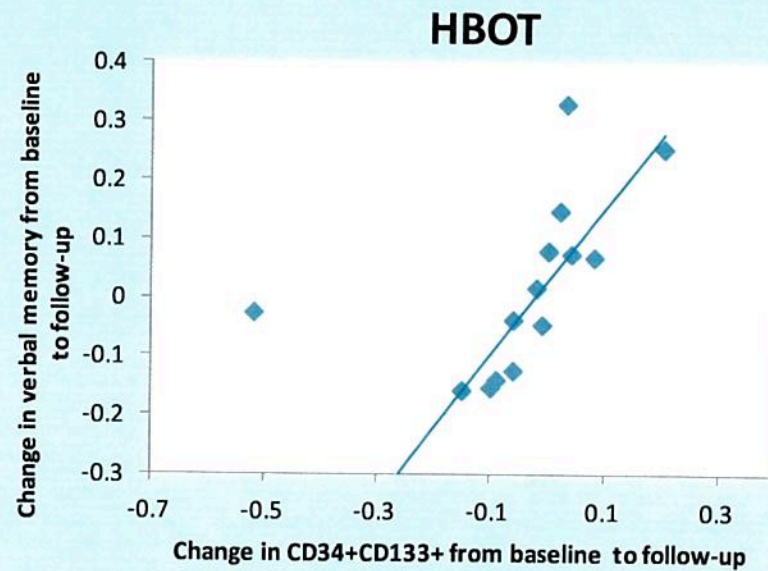
Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy – UHM 44 (3) 2017

Sabrina Shandley, E. George Wolf, Christine M. Schubert-Kabban, et al

- Stem cells collected prior to series, after 15 exposures. after 30 exposure series, and 6 week post series.
- 13 subjects from 1.3 ATA air and 15 subjects from 2.4 ATA O₂
- Nestin is specifically associated with neuronal stem cells.
- CD34 represents a marker for hematopoietic and endothelial stem cells.
- CD133 identified as a marker expressed on hematopoietic stem cells, neural and muscle progenitor cells.

Increased circulating stem cells and better cognitive performance in traumatic brain injury subjects following hyperbaric oxygen therapy – UHM 44 (3) 2017

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- Treatment CD 34+ or nestin are likely a factors in the ImPACT and Braincheckers cognitive changes, but not CD 133+
- CD 133+ is likely the primary stem cell responsible for the PCL-M composite score changes.
- The sham group did not show any statistically significant correlations

Dawn of a New Day

- Oklahoma: Veterans Traumatic Brain Injury Care Improvement Act of 2014
- Indiana: Chapter 13.5. Grants for Veterans' Services
 - Passed effective 1 July 17
 - Service related event within the past 12 months
 - Must pay 10% co-pay of the treatment cost billed
- Texas: Veterans Recovery Pilot Program
 - Provide Veterans with hyperbaric oxygen treatment
 - Passed 29 May 17; effective 1 Sep 17

Comments

- All DoD and civilian published studies have been PILOT STUDIES – safety, efficacy, and focus areas
- Current HBOT indications: only 3 of 14 are primary – all others are adjunctive therapy to standard of care
- HBOT for TBI or PTSD has NEVER been proposed as a primary treatment
- Development of a treatment registry needed
 - Consider criteria (time, cognitive tests, PTSD)
 - Conduct exposures in local areas (study experience)
 - Collect data from variety of exposures vs SOC+crossover
 - Define multiple outcome measures by clinicians

